

APPENDIX B: TOXICOLOGY

Overview

The most comprehensive safety overview conducted to date on HCA, is the study by the Burdock Group published in Food and Chemical Toxicology in 2004.

The most salient conclusions of this study are:

- i. Dried fruit rind of *Garcinia Cambogia* (containing 10-30% HCA) has been used for centuries throughout Southeast Asia as a food preservative, flavouring agent and carminative
- ii. That a brand known as CitriMax (50% HCA as calcium salt) has a low acute oral toxicity
- iii. That the gavage administration of 2500mg/kg/day for a period of 90 days caused a significant decrease in body weight and reduction in feed consumption without any adverse effects
- iv. That the structure, mechanism of action, long history of use of HCA, and other toxicity studies indicate that HCA is unlikely to cause reproductive or developmental effects
- v. In several, placebo-controlled, double blind trials employing up to 2800 mg/day HCA, no treatment-related adverse effects were reported. This level of supplementation is considered to be safe in humans.

In 2003, researchers at Creighton University conducted acute oral toxicity, acute dermal toxicity, primary dermal irritation and primary eye irritation in animals using a HCA extract. Results of this study indicated that the LD50 of HCA-SX (a calcium/potassium salt of 60% HCA extract) is greater than 5,000 mg/kg when administered once orally via gastric intubation to fasted male and female Albino rats. No gross toxicological findings were observed under the experimental conditions.

In 2002, the same researchers also conducted a chronic safety study of HCA. The conclusion of this study was that HCA supplementation did not alter hepatic and testicular lipid peroxidation or DNA fragmentation. The study noted that feed intake was significantly reduced in HCA supplemented rats, demonstrating appetite suppression.

Previous toxicity tests have been conducted to verify the absence of possible side effects or acute/chronic toxicity of the HCA isolate. The results showed that the acute LD50 (Lethal dose for 50% of the animals tested) was greater than 2000 mg/kg for intraperitoneal administration and greater than 4000 mg/kg for oral administration. Researchers at Hoffmann LaRoche achieved very similar results using simple citrate and considered the two compounds almost identical in safety. Acute oral toxicity studies performed at Wil Research Laboratories, Ashland, OH, showed that 5000 mg/kg of Citrimax (brand leader in HCA products) resulted in no toxicity or deaths in rats. This is equivalent to 350 grams, or 233 times the recommended dosage of 1.5grams/day consumed by an average size human. The Merck Index lists the LD50 of citrate used intraperitoneally as 975 mg/kg, which would indicate that HCA is actually safer than citrate.

With regard to safety, the relevant points are as follows:

HCA and citrate are very close in terms of their degree of safety, and the latter is now mostly produced synthetically and widely used in commercial food production.

Citrate is, of course, the primary acid in oranges, lemons and other citrus fruits.

Garcinia Cambogia, the main source of naturally- occurring HCA, has a long history of common use as a flavouring, preservative and herbal tonic. A typical daily dose of HCA in humans for the purpose of losing weight is roughly the equivalent to the rind of half a fruit, which is not out of proportion of its common use. Reports of toxicity do not appear in the literature regarding the traditional use of the extract, so it is highly unlikely that there is any danger from regular consumption.

The most likely negative effect from excess intake of the isolate would be bowel intolerance, and this problem would be reversible through a simple reduction in dosage. This problem was not seen in animal or human studies at the levels of intake, which was necessary to reduce appetite.

Despite its inherent safety, there are individuals who should not use HCA, just as they should not use any other diet product. HCA has been shown to influence the body's own production of cholesterol, and therefore it may influence indirectly the production of sterols. The hormones made from sterols include oestrogen, progesterone, testosterone and so forth. For the great majority of Americans, the diet is so rich in fats and calories in general that a lack of building blocks for fat-dependent hormones within the body is simply not an issue. Nevertheless, some instances do require caution. Pregnancy is a time of extreme sensitivity to steroid hormones, and therefore products, which contain HCA, should not be used during pregnancy. HCA should be avoided during lactation. Similarly, HCA should not be given in large amounts or for extended periods to young children. Although long human experience with fruit sources of HCA does not indicate any danger to these groups, it must be remembered that fruit sources consist almost totally of the less active lactone of HCA

References:

M. G. Soni, G.A. Burdock, H.G. Preuss, S.J. Stohs, S. E. Ohia, D. Bagchi: **Safety assessment of (-)-hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt.** Food and Chemical Toxicology 42 (2004) 1513-1529

Acute oral toxicity, acute dermal toxicity, primary dermal irritation and primary eye irritation in animals using a HCA extract did not cause any gross toxicological findings

Feed intake was significantly reduced in HCA-SX supplemented rats, demonstrating appetite suppression. None of the groups demonstrated any changes in water intake during the 90 days of treatment. HCA-SX supplementation did not alter hepatic and testicular lipid peroxidation or DNA fragmentation. Taken together, these results indicate that HCA-SX is safe and efficacious in weight management under the conditions employed in these studies

Michael Shara, Sunny E. Ohia, Taharat Yasmin, Andrea Zardetto-Smith, Anthony Kincaid, Manashi Bagchi, Archana Chatterjee, Debasis Bagchi and Sidney J. Stohs: **Dose- and time- dependent effects of a novel (-)- hydroxycitric acid extract on body weight, hepatic and testicular lipid peroxidation, DNA fragmentation and histopathological data over a period of 90 days.** Molecular and Cellular Biochemistry 254: 339 –346, 2003

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Clouatre, Dallas and Michael E. Rosenbaum, **The diet and health benefits of HCA (Hydroxycitric Acid)** (New Canaan, CT : Keats Publishing Inc., 1994)

HCA is equivalent to Citrate in Safety of Acute Administration

In vivo study:

"The LD50 values obtained after the intraperitoneal and oral administrations of citrate or (-)-hydroxycitrate to mice were similar >2000 mg/kg for intraperitoneal and greater than 4000 mg/kg for oral administration."

Sullivan, Ann C. and Joseph Triscari (1977a) **Metabolic regulation as a control for lipid disorders. Influence of (-)- hydroxycitrate on experimentally induced obesity in the rodent.** The American Journal of Clinical Nutrition 30, 5 (May 1977) 767-776

Acetylcholine Production In Vitro is Inhibited by both HCA and Citrate, but HCA does Not Cross the Blood-Brain Barrier Nor Directly Influence the Central Nervous System

In vitro studies using rat brain tissue showed that both HCA and citrate inhibit acetylcholine production. Researchers at one time had suggested that some such mechanism might be at work in the appetite-suppressing effects of HCA and that HCA might directly effect a satiety control centre in the brain by this means. However, subsequent studies demonstrated that HCA does not cross the blood brain barrier and that it is not centrally active i.e. it does not influence the Central Nervous System directly. Citrate also decreases acetylcholine production in vitro, but there is no evidence that oral consumption of citrus fruits or other sources of citrate has any negative effects upon in vivo acetylcholine production.

In vitro study:

"... an inhibition [by (-)- hydroxycitrate] of ACh synthesis [in rat caudate nuclei] from glucose and pyruvate has indeed been found, but it was much lower than the inhibition of ACh synthesis from citrate. In addition, it has been found that citrate itself has a strong inhibitory effect on the synthesis of ACh, which is not a consequence of the chelation of Ca^{2+} ions in the incubation medium. In conclusion, the results of experiments with (-)- hydroxycitrate are easier to interpret as evidence against a dominating role of ATP- citrate lyase in the supply of acetyl-CoA for the synthesis of ACh than in favour of such a role.

Tucek, Stanislav, Vladimir Dolezal and Ann C. Sullivan (1981) **Inhibition of the synthesis of acetylcholine in rat brain slices by (-)-hydroxycitrate and citrate.** Journal of Neurochemistry 36,4 (1981) 1331-1337

Review article

"Hydroxycitrate, chlorocitrate, and epoxyaconitate compounds that are structurally similar to the tricarboxylic acid cycle intermediate citric acid, but that differ markedly in biochemical activity have recently been evaluated in animals for effects on appetite. Because neither these compounds or their metabolites enter the brain, their primary effects on food intake occur by peripheral mechanisms"

Sullivan, Ann C and Rhoda K. Gruen (1985) **Mechanisms of appetite modulation by drugs.** Federation Proceedings 44, 1, Part1 (January 1985) 139- 144

HCA does not increase cell respiration nor cause an increase in metabolites

In vitro study:

"...(-)-hydroxycitrate has [sic] little or no effect on respiration, phosphorylation, and citrate accumulation during the course of experiments"

Watson, John A. and John M. Lowenstein (1970). **Citrate and the conversion of carbohydrate into fat.** The Journal of Biological Chemistry 245, 22 (1970) 5993-6002

Animal studies showed no effect on plasma levels on insulin or free fatty acids

Review article:

"No significant differences in plasma levels of glucose, insulin, or free fatty acids were detected in (-)-hydroxycitrate treated rats relative to controls. These data suggest that peripheral metabolism, defined in the present context as metabolite flux, may be involved in appetite regulation..."

Sullivan, Ann C. and Joseph Triscari (1976) **Possible interrelationship between metabolite flux and appetite.** In D. Novin, W. Wyriwicka and G. Bray, eds., *Hunger: Basic Mechanisms and Clinical Implications* (New York: Raven Press, 1976) 115-125

HCA has several mechanisms of action

The Burdock Group, which provides a review of the biochemical/pharmacological effects of HCA states:

“The reported weight reduction effects of HCA are based on its action as a potent and specific inhibitor of the enzyme ATP-citrate lyase (also known as citrate cleavage enzyme), which is required for the synthesis of fatty acids.By inhibiting ATP-citrate lyase at the regulatory juncture of fatty acid metabolism, HCA mimics some of the regulatory activities of citrate. Thus, HCA may decrease the production of fatty acids and cholesterol; slow the glycolytic pathways and consequently increase glycogen production. The decrease in fatty acid synthesis and increase in production of glycogen has a number of biochemical effects.

and

“HCA thus initiates a form of nutrient partitioning as calories are redirected away from fat production and towards glycogen production and storage. This production and storage of glycogen, in turn, influences glucoreceptors, located in the liver, which may induce satiation via the vagus nerve.

Research Paper:

Sullivan A.C. & J. Triscari (~~1976~~)(1977) Novel Pharmacological approaches to the treatment of obesity. In George A. Bray ed., Recent Advances in Obesity Research. II (Westport, Ct: Technomic Publishing Co., 1977) 442-452.